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Canadian Adverse Reaction Newsletter

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Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Contact Health Canada or a Regional AR Centre free of charge

Phone: 866 234-2345
Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

Form available at:

www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf

Withdrawal reactions with paroxetine and other SSRIs

Selective serotonin reuptake inhibitors (SSRIs) are widely used and represent the largest market share of all prescribed antidepressants in Canada.[1] Withdrawal reactions or discontinuation symptoms have been documented with all SSRIs.[2,3] These reactions are clinically relevant because they are common, can cause significant morbidity, may be misdiagnosed, leading to inappropriate treatment, and can adversely affect compliance with future antidepressant treatment.[2] Although defining the true incidence of withdrawal reactions associated with SSRIs is problematic, Canadian adverse reaction (AR) data along with spontaneous AR data from Australia, France, the United Kingdom and the United States reveal that withdrawal reactions are reported more frequently with paroxetine than with other SSRIs.[4-7]

Although the mechanism of the SSRI withdrawal syndrome is not completely understood, the onset, frequency and intensity of the symptoms seem to vary according to the pharmacologic and pharmacokinetic properties of the drug, such as the half-life (major risk factor), the presence of active metabolites and the anticholinergic effects of the agent.[3,8] Compared with other SSRIs, paroxetine has a short half-life, no active metabolite, a greater anticholinergic effect and greater potency in blocking serotonin reuptake, which could be seen as contributing factors.[3,5]

The withdrawal symptoms may occur after the treatment is stopped, the dose is reduced, the treatment is switched to another antidepressant, or doses are missed.[2,3,9] With paroxetine, symptoms occurred and became statistically significant as early as the second dose of placebo in a study evaluating the interruption of SSRI treatment.[8] The symptoms observed following SSRI discontinuation can either be physical or psychological and are often grouped into the following categories: disequilibrium (e.g., dizziness, vertigo, ataxia), gastrointestinal disturbances (e.g., nausea, vomiting), influenza-like symptoms (e.g., fatigue, lethargy, myalgia), sensory disturbance (e.g., paresthesia), sleep disorder (e.g., insomnia, vivid dreams) and psychiatric disturbance (e.g., anxiety, agitation, confusion).[9,10] Withdrawal symptoms can easily be misdiagnosed as recurrence of depression, evidence of ineffectiveness of the antidepressant in a noncompliant patient, or adverse reactions of the new antidepressant following a switch of medication.[2] Most withdrawal reactions are mild and transient, usually occurring within 1–3 days (up to 1 week) after stopping the medication and lasting 7–14 days, but occasionally the symptoms last for several weeks.[2,9] However, some reactions can be severe and may require acute treatment.[9]

The October 1998 issue of this newsletter outlined a summary of

Newsletter and Advisories by email

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26 Canadian reports of suspected withdrawal reactions associated with SSRIs.[10] Health Canada continues to receive spontaneous reports of such reactions for each SSRI, and Table 1 outlines these reports from the time each SSRI was marketed in Canada to Oct. 31, 2002. There were 102 reports of suspected withdrawal reactions (citalopram [5], fluoxetine [6], fluvoxamine [2], paroxetine [79] and sertraline [10]), and 49% were identified as serious. Table 2 outlines the symptoms described in these reports.

General strategies to prevent and manage symptoms associated with the discontinuation of SSRIs have been outlined previously in this newsletter and include a gradual tapering of the dose when discontinuing treatment with any SSRI except for fluoxetine.[10] If withdrawal reactions occur while tapering or at the end of treatment, it may be necessary to increase the dose and initiate a slower rate of taper.[2,3] Some authors suggest switching to fluoxetine if symptoms are severe and the patient is unable to discontinue the SSRI despite tapering.[2,10,11] For paroxetine, some suggest reducing the dose by 5 mg/d at weekly intervals to below the initial minimum therapeutic dose.[9]

Clinicians should be aware that the use of an antidepressant with a short half-life may be an important risk factor for withdrawal reactions.[9] Patients should be informed of the risks of withdrawal reactions on initiation of therapy to prevent unguided cessation of treatment. Proper diagnosis of withdrawal reactions may prevent unnecessary reinstatement of long-term antidepressant treatment, unnecessary tests to elucidate an underlying problem or an undesirable escalation of dose.

Table 1: Reports submitted to Health Canada of suspected withdrawal syndrome associated with SSRIs from date marketed to Oct. 31, 2002*

Variable	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Date marketed in Canada	1999	1989	1991	1993	1992
Total no. of AR reports	172	1363	198	940	480
No. of reports with suspected withdrawal reactions	5	6	2	79	10
Half-life†	33–66 h	1–9 d	12–22 h	10–26 h	26 h
Active metabolites†‡	–	Norfluoxetine	–	–	N-desmethyl-sertraline

Note: SSRI = selective serotonin reuptake inhibitor, AR = adverse reaction.
***These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between products because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**
†Information from reference 7.
‡Norfluoxetine has similar activity as fluoxetine, N-desmethylsertraline has minimal activity.

Table 2: Symptoms described in the 102 reports submitted to Health Canada of suspected withdrawal syndrome associated with SSRIs from date marketed to Oct. 31, 2002*

	Drug; no. of reactions				
Symptom	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Disequilibrium†	2	2	–	49	4
Gastrointestinal disturbance‡	1	–	2	35	5
Influenza-like symptom§	–	2	2	24	3
Sensory disturbance¶	1	1	–	27	1
Sleep disorder**	1	–	–	17	1
Psychiatric disturbance††	12	7	2	94	10
Other	–	–	–	14	–
Vision disorder	–	2	2	11	1
Headache	–	1	–	11	–
Sweating increased	1	–	–	8	1
Palpitations or tachycardia	–	1	1	6	1
Tremor	–	1	–	64	5
Miscellaneous‡‡	4	1	–	64	5
Total reactions*	22	17	9	360	32

***These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between products because ARs are under reported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.** Several reaction terms may be listed per AR report. Reaction terms are based on the "preferred term" of the World Health Organization (WHO) *Adverse Reaction Dictionary* (WHOART).
†Includes ataxia, dizziness, abnormal gait and vertigo.
‡Includes abdominal pain, diarrhea, dyspepsia, nausea and vomiting.
§Includes asthenia, chills, fatigue, fever, lethargy, myalgia and malaise.
¶Includes paresthesia (electric shock sensation) and hypoesthesia.
**Includes insomnia and abnormal dreaming.
††Includes aggressive reaction, agitation, anxiety, impaired concentration, confusion, depression, depersonalization, hallucination, manic reaction, paranoid reaction, somnolence and suicidal tendency.
‡‡Includes, but not limited to, dystonia, dyskinesia, extrapyramidal disorder, involuntary muscle contractions, convulsions and speech disorder.

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Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

Adverse reaction reporting — 2002

Health Canada received 8566 domestic reports of suspected ARs to health products in 2002. The ARs were reported for the most part by health professionals (pharmacists, physicians, nurses, dentists, coroners and others), either directly to Health Canada or indirectly through another source (Table 1). A further analysis of the total number of reports by reporter type (originator) is outlined in Table 2. The proportion of reports submitted by patients and consumers has increased steadily in recent years.

Of the AR reports received, 5889 were classified as serious. A serious AR is defined in the Food and Drugs Act and Regulations as "a noxious and unintended response to a drug which occurs at any dose and requires inpatient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death."

A steady increase in the reporting of ARs in Canada over the past 5 years has been noted, with 15.9% more reports in 2002 than in 2001 (Fig. 1).

Health Canada would like to thank all who have contributed to the program and encourages the continued support of postmarketing surveillance through AR reporting. Since 2001, health professionals and consumers may report ARs by using the toll-free telephone (866 234-2345) and fax (866 678-6789) lines. Your call will be directed to the appropriate Regional AR Centre. Manufacturers must continue to report ARs using the established fax line 613 957-0335.

Lynn Macdonald, BSP, Health Canada

Table 1: Source of reports of adverse reactions (ARs) received by Health Canada in 2001 and 2002

	No. (and %) of reports received	
Source	2001	2002
Manufacturer	4752 (64.3)	5794 (67.6)
Regional AR Centre	2373 (32.1)	2529 (29.5)
Other*	264 (3.6)	243 (2.8)
Total	7389 (100.0)	8566 (100.0)

*Includes, but not limited to, professional associations, nursing homes, hospitals, physicians, pharmacists, Health Canada regional inspectors, coroners, dentists and patients

Table 2: Number of AR reports by type of reporter (originator) in 2001 and 2002

	No. (and %) of reports	
Reporter	2001	2002
Pharmacist	2097 (28.4)	2141 (25.0)
Physician	1914 (25.9)	2093 (24.4)
Health professional*	1378 (18.6)	1780 (20.8)
Consumer/ patient	1102 (14.9)	1581 (18.5)
Nurse	443 (6.0)	421 (4.9)
Other	455 (6.2)	550 (6.4)
Total	7389 (100.0)	8566 (100.0)

*Type not specified in report

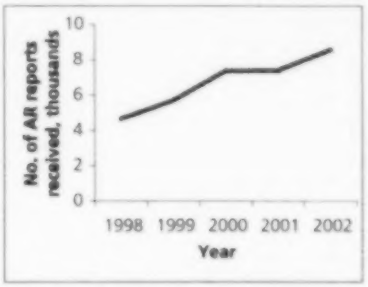

Fig. 1: Number of reports of adverse reactions received annually by Health Canada from 1998 to 2002.

Case Presentation

Recent cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Please report similar reactions.

Divalproex

A 14-year-old girl (weight 59 kg) with a history of absence seizures was prescribed divalproex sodium therapy in anticipation of obtaining her driver's licence. When the patient started taking the anticonvulsant, she began to withdraw socially. With 3 subsequent dosing increments to control the seizures, she became increasingly depressed, suicidal and then psychotic. The dosages and ARs were reported as follows:

Aug 2000: dose: 375 mg orally twice daily to initiate therapy; ARs: social withdrawal, described as "not as sharp"
Oct 2000: dose: 500 mg orally twice daily; ARs: increasing signs of depression
Feb 2001: dose: 625 mg orally twice daily; ARs: suicidal ideation, suicide attempt (Apr 2001), emotional volatility, confrontational behaviour
Aug 2001: dose: 625 mg orally in the morning, 750 mg in the evening; ARs: delusional reaction, paranoid reaction, hostile and threatening behaviour, self-mutilation, cognitive difficulties

The patient was admitted to hospital twice in May 2001 and again in October 2001. She was treated with citalopram (Celexa) 20 mg/d from May to September 2001 and then 40 mg/d to October 2001. In addition, the patient attended weekly psychotherapy sessions and in October 2001 received a few doses of quetiapine (Seroquel). During the third admission to hospital, the divalproex treatment was stopped at the request of her parents. The divalproex was tapered over 5 weeks, and the other drugs were also stopped. The problems gradually resolved after the divalproex was discontinued; the drug was not reintroduced. The patient had not been treated for depression or other psychiatric disorders before starting the anticonvulsant therapy.

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The safe use of products containing acetaminophen

In an effort to inform consumers about the risks of taking multiple acetaminophen-containing preparations simultaneously, Health Canada has issued a Public Advisory (www.hc-sc.gc.ca/english/protection/warnings/2003/2003_06.htm). In addition, Health Canada has posted an "It's Your Health" document that outlines the safe use of all medications (www.hc-sc.gc.ca/english/iyh/medical/safe_medicine.html). These documents advise consumers on ways to minimize the risk of adverse effects associated with medications, which include carefully reading the labels of all medications and consulting with their health care professional. We encourage health care professionals to share the above information with their patients.

"It's Your Health": hormone replacement therapy

Recent studies have raised questions about the long-term safety of combined estrogen and progestin hormone replacement therapy (HRT). Health Canada has posted an "It's Your Health" document on its Web site (www.hc-sc.gc.ca/english/iyh/medical/estrogen.html) that summarizes the health risks and benefits of HRT that were reported from studies included in the Women's Health Initiative of the United States National Institutes of Health. The decision to use HRT should be based on the individual patient's needs and health, following a medical evaluation and a discussion of the benefits and risks with a physician.

Summary of health professional and consumer advisories posted since Nov. 27, 2002
(advisories are available at www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/adv.hp_e.html and www.hc-sc.gc.ca/english/protection/warnings/2003.html)

Date	Product	Subject and type
Feb 18	Ergotamine/ dihydroergotamine	New contraindications for medications containing ergotamine and dihydroergotamine — Novartis Pharmaceuticals Canada Inc. — consumer information
Feb 17	Cochlear implants	Recipients may be at greater risk for meningitis — information update — health professional advisory
Feb 13	Acetaminophen-containing products	Health Canada is advising Canadians about the safe use of products containing acetaminophen — consumer information
Jan	Ergotamine/ dihydroergotamine	New contraindication regarding ergotamine- and dihydroergotamine-containing drugs: risk of cerebral and/or peripheral ischemia — Novartis Pharmaceuticals Canada Inc. — health professional advisory
Dec	Bextra	Serious skin reactions and cases of hypersensitivity reactions — Pharmacia and Pfizer — health professional advisory
Dec 19	Diane-35	Important safety concerns on the use of Diane-35 — health professional advisory
Dec 17	Kineret	Use of Kineret (anakinra) in combination with etanercept — Amgen Canada Inc. — health professional advisory and consumer information
Dec 16	Synagis	Important information on Synagis (palivizumab) — Abbott Laboratories — health professional advisory
Dec 12	Accolate	Liver problems associated with use of Accolate in some patients — AstraZeneca — consumer information
Oct 7	Accolate	Important safety information regarding Accolate and hepatic effects — AstraZeneca — health professional advisory

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Suggestions?
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